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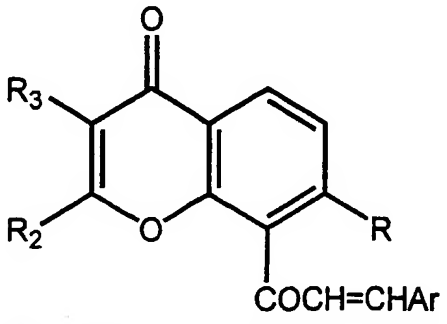
(54) Title: NOVEL CHALCONES



(I)

(57) Abstract: Disclosed are novel chalcone derivatives having Formula (I). The compounds possess antiproliferative activity, and are useful for the manufacture of a medicament for the treatment or prevention of neoplasms, particularly those located in the uterus, ovary or breast. The compounds of the invention may also be useful in the manufacture of a medicament for the treatment or prevention of menopausal disorders and osteoporosis.

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NOVEL CHALCONES

The present invention relates to a novel class of compounds which have structures related to certain naturally occurring and synthetic chalcones, as well as to methods for the preparation of such compounds and to pharmaceutical uses thereof.

The compound 1,3-diphenyl-2-propene-1-one is known by the trivial name "chalcone". Many naturally occurring flavonoids share structural features with chalcone and are referred to by the generic term "chalcones". Also, certain flavonoids, including ones which are also classified as chalcones, have recently been demonstrated to have anticancer activity (Cancer Research 48, 5754, 1988) and chemopreventive activity in some tumours (J. Nat. Prod. 53, 23, 1990).

In particular, quercetin, an ubiquitous flavonoid found in plants, has been shown to act on the proliferation of human leukaemic cells (Br. J. Haematology, 75, 489, 1990) and on other cell lines (Br. J. Cancer, 62, 94, 942, 1990; Int. J. Cancer, 46, 112. 1990; Gynaecologic Oncology, 45, 13, 1992) and to possess a synergic action with common antiblastic drugs.

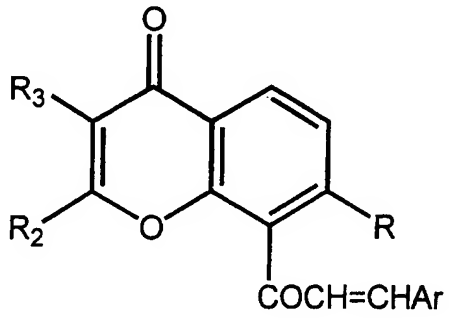
In addition, some natural or synthetic chalcones, described in our International Patent Publication No. WO 91/17749, and in International Patent Publication No. WO 96/19209 (Baylor College of Medicine), have proved to have a significant antiproliferation activity on a variety of different cell lines.

Although the mechanism of action of the antiproliferative activity of flavonoids and chalcones is still unknown, it is believed to be linked to the interaction of these compounds with type II oestrogen receptors.

The action *in vivo* of these polyphenol substances is certainly much more complicated. All these compounds are generally characterised by an almost complete insolubility in water and, *in vivo,* by a very poor bioavailability linked to a rapid metabolism of phenols and a marked affinity for lipids and proteins.

Surprisingly, it has now been found that certain novel chalcones, chalcone derivatives and chalcone analogues, and in particular, compounds in which the phenyl ring in the 1-position is substituted or replaced by rings containing one or more heteroatoms, possess a greater antiproliferation activity both on sensitive cancerous cells and on cells which are resistant to common chemotherapeutic drugs, including the latest generation anti-neoplastic agents, paclitaxel and docetaxel.

Thus according to one aspect of the present invention, there is provided a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt or solvate thereof wherein:

Ar represents

a substituted or unsubstituted, (preferably aromatic), carbocyclic or heterocyclic group, said carbocyclic or heterocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings, wherein the or each ring contains 5 or 6 ring atoms, any heteroatoms

being selected from N, O and S, any substituents on the Ar group being independently selected from the group consisting of:

(a) Cl, (b) Br, (c) F, (d) OH, (e) NO_2, (f) CF_3, (g) C_{1-4} lower alkyl (in particular CH_3), (h) SCH_3, (i) $NHCOCH_3$, (j) $N(R^6)(R^8)$ wherein R^6 and R^8 are the same or different and each represents H or lower C_{1-4} alkyl, (k) OR^{10} wherein R^{10} represents a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from:

Cl, Br, F, OMe, NO_2 and CF_3,

and (l) $-OCOR^{11}$, wherein R^{11} represents a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group or a phenyl group;

R represents

OH, OR^{10} or $OCOR^{11}$, wherein R^{10} and R^{11} are as defined above; and

(A) R^2 and R^3 are each independently selected from:

(i) a substituted or unsubstituted, preferably aromatic, carbocyclic or heterocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings, wherein the or each ring contains 5 or 6 ring atoms, any heteroatoms being selected from N, O and S, any substituents being independently selected from the group consisting of:

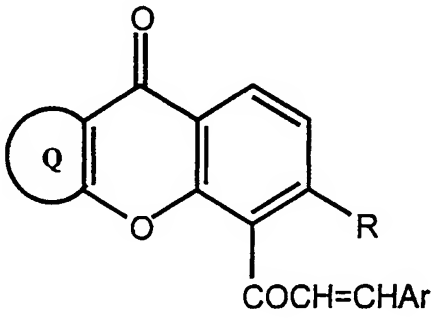
Cl, Br, F, OH, NO_2, CF_3, C_{1-4} lower alkyl (in particular CH_3), SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $OCOR^{11}$, wherein R^6, R^8, R^{10} and R^{11} are as defined above,

(ii) Cl, (iii) Br, (iv) F, (v) OH, (vi) NO_2, (vii) a saturated or unsaturated lower C_{1-4} straight or branched hydrocarbyl group which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3, (viii) $NHCOCH_3$, (ix) $N(R^6)(R^8)$, (x) SR^{10}, (xi) OR^{10}, and (xii) $OCOR^{11}$ wherein R^6, R^8, R^{10} and R^{11} are as defined above;

or

(B) R_2 and R_3 taken together with the carbon atoms to which they are attached form a carbocyclic or heterocyclic ring having 5 or 6 ring atoms, any heteroatom being selected from N, O or S, said carbocyclic or heterocyclic ring being saturated or unsaturated, and being unsubstituted or substituted with one or more substituents selected from Cl, Br, F, OH, NO_2, CF_3, C_{1-6} lower alkyl, SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $OCOR^{11}$, wherein R^6, R^8, R^{10} and R^{11} are as defined above.

Compounds described above, wherein R_2 and R_3 taken together with the carbon atoms to which they are attached form a ring, may be represented by Formula (IA):



(IA)

wherein the substituents R and Ar are as defined above, and R^2 and R^3 taken together represent Ring Q, said Ring Q being a five- or six-membered, preferably aromatic, carbocyclic or heterocyclic ring, any heteroatom being selected from N, O, or S, said ring being unsaturated or saturated, said carbocyclic ring or heterocyclic ring may be unsubstituted or substituted with one or more substituents selected from: Cl, Br, F, OH, NO_2, CF_3, C_{1-4} lower alkyl, SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $OCOR^{11}$, wherein R^6, R^8, R^{10} and R^{11} are as defined for Formula (I).

Compounds of the invention having a structure Formula (IA) represent the xanthone derivatives of the present invention.

The present invention also embraces compounds of Formula (I), wherein R and Ar are as defined for Formula (I) above and wherein R^2 and R^3 are each independently selected from:

(i) a substituted or unsubstituted, preferably aromatic, carbocyclic or heterocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings, wherein the or each ring contains 5 or 6 ring atoms, any heteroatoms being selected from N, O and S, any substituents being independently selected from the group consisting of:

Cl, Br, F, OH, NO_2, CF_3, C_{1-4} lower alkyl (in particular CH_3), SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $OCOR^{11}$, wherein R^8, R^8, R^{10} and R^{11} are as defined above,

(ii) Cl, (iii) Br, (iv) F, (v) OH, (vi) NO_2, (vii) a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3, (viii) $NHCOCH_3$, (ix) $N(R^6)(R^8)$, (x) SR^{10}, (xi) OR^{10}, and (xii) $OCOR^{11}$ wherein R^6, R^8, R^{10} and R^{11} are as defined above.

Such compounds include flavone derivatives according to the present invention. One preferred class of compounds according to Formula (I) are those wherein Ar, R and R^3 are as defined in the above paragraph and wherein R^2 represents

a substituted or unsubstituted, preferably aromatic, carbocyclic or heterocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings, wherein the or each ring contains 5 or 6 ring atoms, any heteroatoms being selected from N, O and S, any substituents being independently selected from the group consisting of:

Cl, Br, F, OH, NO_2, CF_3, C_{1-4} lower alkyl (in particular CH_3), SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $OCOR^{11}$, wherein R^6, R^8, R^{10} and R^{11} are as defined as for Formula (I) above,

represent flavone derivatives according to the present invention.

Preferably for the above described compounds, R^3 is selected from the group consisting of:

Cl, Br, F, OH, NO_2, a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from:

Cl, Br, F, OMe, NO_2 and CF_3;

$NHCOCH_3$, $N(R^6)(R^8)$, SR^{10}, OR^{10} and $OCOR^{11}$, wherein R^6, R^8, R^{10} and R^{11} are as defined for Formula (I) above.

In a further preferred group of compounds according to the present invention, R^2 represents:

a substituted or unsubstituted, preferably aromatic, carbocyclic or heterocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings, wherein the or each ring contains 5 or 6 ring atoms, any heteroatoms being selected from N, O and S, any substituents being independently selected from the group consisting of:

Cl, Br, F, OH, NO_2, CF_3, C_{1-4} lower alkyl (in particular CH_3), SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $OCOR^{11}$, wherein R^6, R^8, R^{10} and R^{11} are as defined in Claim 1; and

R^3 is selected from the group consisting of:

Cl, Br, F, OH, NO_2, a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from:

Cl, Br, F, OMe, NO_2 and CF_3,

$NHCOCH_3$, $N(R^6)(R^8)$, SR^{10}, OR^{10} and $OCOR^{11}$, wherein R^6, R^8, R^{10} and R^{11} are as defined above.

A further preferred group of compounds according to the present invention include compounds wherein

R^3 is selected from:

Cl, Br, F, OH, NO_2, CF_3, C_{1-4} lower alkyl, SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10}, and $OCOR^{11}$ wherein R^6, R^8, R^{10} and R^{11} are as defined for Formula (I) above.

A particularly preferred R^3 group is C_{1-4} lower alkyl, especially methyl.

In a further preferred class of compounds, R^2 preferably represents a substituted or unsubstituted (preferably aromatic) carbocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings, wherein the or each ring contains 5 or 6 ring atoms, and any substituents are independently selected from the group consisting of:

Cl, Br, F, OH, NO_2, CF_3, C_{1-4} lower alkyl (in particular CH_3), SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $OCOR^{11}$, wherein R^6, R^8, R^{10} and R^{11} are as defined above.

Of these, R^2 preferably represents an unsubstituted, preferably aromatic, carbocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings. An especially preferred R^2 group is phenyl.

For the compounds of Formula (I), Ar preferably represents phenyl which may be unsubstituted or substituted with one or more substituents selected from the group consisting of Cl, Br, F, OH, NO_2, CF_3, C_{1-4} lower alkyl (in particular CH_3), SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $OCOR^{11}$ wherein R^6, R^8, R^{10} and R^{11} are as defined for Formula (I).

Particularly preferred Ar groups include phenyl or phenyl substituted with 1, 2 or 3 methoxy groups.

For the Ar, R^2 and R^3 groups of Formula (I), the R^{10} and R^{11} groups are preferably a saturated or unsaturated C_{1-6} straight chain or branched hydrocarbyl group. Particularly preferred groups include methyl, ethyl, n-propyl and iso-propyl. An especially preferred group is methyl.

The group R of the compounds of the invention preferably represents the group OR^{10}. Within this group of compounds, preferred OR^{10} groups include $-OCH_2CH=CMe_2$, $-OCH_2CMe=CH_2$, $-OCH_2CH=CH_2$ and $-OCH_2C\equiv CH$.

A further preferred group of compounds of the invention are compounds of Formula (I) wherein

Ar represents

phenyl, which may be unsubstituted or substituted by one, two or three substituents independently selected from

Cl, Br, F, OMe, NO_2, CF_3, C_{1-4} lower alkyl (in particular CH_3), NMe_2, NEt_2, SCH_3 and $NHCOCH_3$;

thienyl, 2-furyl, 3-pyridyl, 4-pyridyl or indolyl; and

R represents

OH or OCH_2R^1, wherein R^1 is selected from $-CH=CMe_2$, $-CMe=CH_2$, $-CH=CH_2$ and $-C\equiv CH$.

Within this group of compounds, Ar is preferably selected from trimethoxyphenyl, 3-pyridyl, 4-pyridyl and 3-indolyl, and R is preferably selected from $OCH_2CH=CMe_2$, $OCH_2CMe=CH_2$, $OCH_2CH=CH_2$ and $OCH_2C\equiv CH$.

In a preferred class of compounds, Ar contains a basic nitrogen function, for example, by virtue of a heterocyclic nitrogen ring atom being present, or Ar may contain a substituent having a basic nitrogen, such as an amine, or an acetamido function. Thus a preferred Ar group is a substituted or unsubstituted, preferably aromatic, heterocyclic group, said heterocyclic group containing from 5 to 10 ring atoms, at least one of which is a nitrogen atom, said ring atoms forming one or two rings, with the or each ring containing 5 or 6 ring atoms, wherein any substituent on the ring is as defined as for Formula (I). A further preferred group of compounds is wherein the group Ar is substituted with at least one substituent selected from $NHCOCH_3$ or $N(R^6)(R^8)$, wherein R^6 and R^8 are the same or different and each represents H or lower C_{1-4} alkyl.

Particularly preferred Ar groups containing a basic nitrogen function include of 3-pyridyl, 4-pyridyl, 3-indolyl, 4-dimethylaminophenyl and 4-acetamidophenyl.

It will be appreciated that compounds of Formula (I) which contain a basic amino function may be converted to acid addition salts, with pharmacologically acceptable acids, e.g. hydrochloric acid and phosphoric acid. Such salts are also included in the present invention.

The present invention also provides the use of a compound of Formula (I) in the manufacture of an antiproliferative medicament. In particular, the compounds of the present invention may be useful for the manufacture of a medicament for the treatment or prevention of neoplasms, particularly those located in the uterus, ovary or breast. In particular, the compounds may be useful for the manufacture of a medicament for the treatment of cancer cells that are resistant to paclitaxel and docetaxel.

The compounds of Formula (I) may advantageously be used in combination therapies involving the combined use of a compound of Formula (I) and another anti-neoplastic agent, especially paclitaxel or docetaxel. The combination therapy may involve simultaneous or successive administration of a compound of Formula (I) and an anti-neoplastic agent. Such combination therapy forms a further aspect of the invention.

The compounds of the invention may be further used in the manufacture of a medicament for the treatment or prevention of menopausal disorders and osteoporosis.

The present invention further includes a pharmaceutical composition comprising one of more of the compounds of Formula I in combination with one or more pharmaceutically acceptable excipients.

The invention will now be described by way of illustrative examples and with reference to the accompanying formulae drawings.

EXAMPLES

Example 1. General conditions to obtain chalcones.

Method A.

A solution of KOH 50% (3 ml) is added to an equimolar solution of acetophenone (0.0075 mol) and aldehyde (0.0075 mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified; the precipitate is separated by filtration and dried under vacuum. The compounds are crystallized by ethanol or first separated by chromatography and then crystallized by ethanol.

Method B.

A solution of acetophenone (0.0075 mol), aldehyde (0.0075 mol), piperidine (15 ml) and acetic acid (75 ml) in ethyl alcohol 95% (80 ml) is countercurrent heated for 5 hours. Molecular sieves are added to the solution to eliminate water and the whole is left at rest for one night. The precipitate that is generally obtained is gathered and crystallized. If the product does not precipitate in these conditions, the solvent is vacuum evaporated and the residue is purified by chromatography on silica gel column.

Example 2. 1-[3-(3-Methylbut-2-enyloxy)xanthen-9-one-4-yl]-3-phenyl-propen-1-one (see accompanying formula drawing VIB 176).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 3-(3-methylbut-2-enyloxy)-4-acetylxanthen-9-one (2.4 g, 0.0075 mol) and benzaldehyde (0.8 g, 0.0075 mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified; the precipitate is

separated by filtration and dried under vacuum. The compound is crystallized by methanol to give 2.1 g of product m.p. 116-118°C, ^{1}H-NMR (CDCl3)δ:1.69 (s, 3H); 1.72 (s, 3H); 4.71 (d, 2H, J = 6.5); 5.38-5.40 (m, 1H); 7.05-7.10 (m, 2H); 7.08 (d, 1H, J = 8.8 Hz); 7.10 (d, 1H, J = 16 Hz); 7.30-7.48 (m, 6H); 7.50-7.58 (m, 2H); 7.65-7.60 (m, 1H)
8.30-8.33(m, 1H); 8.42 (d, 1H, J = 8.9 Hz).

Example 3. 1-[3-(3-Methylbut-2-enyloxy)xanthen-9-one-4-yl]-3-(3-methoxy-phenyl)-propen-1-one (see accompanying formula drawing VIB 177).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 3-(3-methylbut-2-enyloxy)-4-acetylxanthen-9-one (2.4 g, 0.0075 mol) and 3-methoxy-benzaldehyde (1.01 g, 0.0075 mol) in ethanol 95%, the addition being performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified. The precipitate is separated by filtration and dried under vacuum. The compound is crystallized with methanol to give 1.9 g of product m.p. 134-36°C, ^{1}H-NMR ($CDCl_3$) δ: 1.69 (s, 3H); 1.72 (s, 3H); 3.84 (s, 3H); 4.71 (d, 2H, J = 6.5); 5.38-5.40 (m, 1H); 6.95-6.98 (m, 1H); 7.05-7.15 (m, 2H); 7.08 (d, 1H, J = 8.8 Hz); 7.09 (d, 1H, J = 16 Hz); 7.23-7.42 (m, 4H); 7.65-7.72 (m, 1H); 8.32-8 (d, 1H, J = 8.8 Hz); 8.42(d, 1H, J = 8.9 Hz).

Example 4. 1-[3-(3-Methylbut-2-enyloxy)xanthen-9-one-4-yl]-3-(3,4,5-trimethoxyphenyl)-propen-1-one (see accompanying formula drawing VIB 178).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 3-(3-methylbut-2-enyloxy)-4-acetylxanthen-9-one (2.4 g, 0.0075 mol) and 3, 4, 5-trimethoxy-benzaldehyde (1.47 g, 0.0075 mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified; the precipitate is separated by filtration and dried under vacuum. The compound is

crystallized by methanol to give 2.2 g of product m.p. 153-55°C, ^{1}H NMR ($CDCl_3$) δ:1.69 (s, 3H); 1.72 (s, 3H); 3.85-3.91 (m, 9H); 4.73 (d, 2H, J = 6.5); 5.38-5.40 (m, 1H); 6.78 (s, 2H); 7.03 (d, 1H, J = 16 Hz); 7.09 (d, 1H, J = 8.8 Hz); 7.23-7.42 (m, 2H); 7.27 (d, 1H J=16 Hz); 7.80-7.87; (m, 1H) ; 8.32 (d, 1H, J = 8.8 Hz); 8.44 (d, 1H, J = 8.9 Hz).

Example 5. 1-[3-(allyloxy)xanthen-9-one-4-yl] -3-phenyl-propen-1-one (see accompanying formula drawing VIB 175).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 3-allyloxy-4-acetylxanthen-9-one (2.2 g, 0.0075 mol) and benzaldehyde (0.8 g, 0.0075 mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified; the precipitate is separated by filtration and dried under vacuum. The compound is crystallized by methanol to give 2 g of product m.p. 150-152°C, ^{1}H-NMR ($CDCl_3$) δ: 4.73-4.74 (m, 2H); 5.25-5.42 (m, 2H); 5.92-6.05 (m, 1H); 7.07 (d, 1H, J = 8.9 Hz); 7.13 (d, 1H, J = 16 Hz); 7.36-7.44 (m, 6H); 7.52-7.60(m, 2H); 8;31-8.36 (m, 1H); 8.43 (d, 1H, J = 8.9 Hz).

Example 6. 1-[3-methyl-7-(3-methylbut-2-enyloxy)flavon-8-yl]-3-phenyl-propen-1-one (see accompanying formula drawing VIB 166).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 7-(3-methylbut-2-enyloxy)-8-acetyl-3-methylflavone (2.71 g, 0.0075 mol) and benzaldehyde (0.8 g, 0.0075 mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified; the precipitate is separated by filtration and dried under vacuum. The compound is crystallized by methanol to give 2.3 g of product m.p. 83-84°C, ^{1}H-NMR ($CDCl_3$) δ:1.67 (s, 3H); 1.70 (s, 3H); 2.18 (5, 3H); 4.68 (d, 2H, J = 6.4 Hz); 5.30-5.38 (m, 1H); 7.00 (d, 1H, J =16 Hz); 7.02 (d, 1H, J = 8.9 Hz; 7.24 (d, 1H, J = 16 Hz); 7.30-7.45 (m, 6H); 7.48-7.54 (m, 4H);8.30 (d, 1H , J = 8.9 Hz).

Example 7. 1-[3-methyl-7-(3-methylbut-2-enyloxy)flavon-8-yl]-3-(3-methoxy)phenyl-propen-1-one (see accompanying formula drawing VIB 170).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 7-(3-methylbut-2-enyloxy)-8-acetyl-3-methylflavone (2.71 g, 0.0075 mol) and 3-methoxy-benzaldehyde (1.01 g, 0.0075 mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified; the precipitate is separated by filtration and dried under vacuum. The compound is crystallized by methanol to give 2.2 g of product m.p. 134-36°C, ^{1}H-NMR (CDCl3) δ:1.67 (s, 3H); 1.70 (s, 3H); 2.18 (s, 3H); 3.82 (s, 3H) 4.68 (d, 2H, J = 6.4 Hz); 5.30-5.38 (m, 1H);6.93 (d, 1H, J = 16 Hz,); 6.96-7;18 (m, 3H);7.09 (d, 1H, J = 8,9 Hz); 7.20 (d, 1H, J = 16 Hz) 7,23-7.30 (m, 1H); 7.35-7.45 (m, 3H); 8.30 (d, 1H, J =8.9 Hz).

Example 8. 1-[3-methyl-7-(3-methylbut-2-enyloxy)flavon-8-yl]-3-(3,4,5-trimethoxy)phenyl-propen-1-one (see accompanying formula drawing VIB 173).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 7-(3-methylbut-2-enyloxy)-8-acetyl-3-methylflavone (2.71 g, 0.0075 mol) and 3,4,5-trimethoxy-benzaldehyde (1.47 g, 0.0075 mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified; the precipitate is separated by filtration and dried under vacuum. The compound is crystallized by methanol to give 2 g of product m.p.153-55°C, ^{1}H-NMR ($CDCl_3$) δ:1.70 (s, 3H); 1.72 (s, 3H); 2.18 (s, 3H); 3.86-3.91 (m, 9H); 4.70 (d, 2H, J = 6.4 Hz); 5.34-5.42 (m, 1H); 6.73 (s, 2H); 6.93 (d, 1H, J = 16 Hz); 7.09 (d, 1H, J = 8.9 Hz); 7.22 (d, 1H, J = 16 Hz); 6,96-7;18 (m, 3H); 7.52-7.58 (m, 2H); 8.32 (d, 1H, J = 8.9 Hz).

Example 9. 1-[3-methyl-7-(allyloxy)flavon-8-yl]-3-phenyl-propen-1-one (see accompanying formula drawing VIB 164).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 7-allyloxy-8-acetyl-3-methylflavone (2.5 g, 0.0075 mol) and benzaldehyde (0.8 g, 0.0075 mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified; the precipitate is separated by filtration and dried under vacuum. The compound is crystallized by methanol to give 2.3 g of product m.p.145-47°C, ^{1}H-NMR (CDCl3) δ:1.77 (s, 3H); 2.20 (s, 3H); 4.73 (d, 2H, J = 5.1 Hz); 5.25-5.45 (m, 2H); 5.91-6.02 (m, 1H); 7.05 (d, 1H, J = 16 Hz); 7.11 (d, 1H, J = 8.9 Hz); 7.38-7.48 (m ,7H); 7.53-7.59 (m, 4H); 8.34 (d, 1H, J = 8.9 Hz).

Example 10. 1-[3-methyl-7-(allyloxy)flavon-8-yl)-3-(3-methoxyphenyl)-propen-1-one (see accompanying formula drawing VIB 168).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 7-allyloxy-8-acetyl-3-methylflavone (2.5 g, 0.0075 mol) and 3-methoxy-benzaldehyde (1.01 g, 0.0075 mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified; the precipitate is separated by filtration and dried under vacuum. The compound is crystallized by methanol to give 2.4 g of product m.p.90-92°C, ^{1}H-NMR ($CDCl_3$) δ: 2.20 (s, 3H); 3.84 (s, 3H); 4.74 (d, 2H, J = 5,1 Hz); 5.1-5.3 (m, 2H); 5.91-6.02 (m, 1H); 6.96-7.18 (m, 4H); 7.31 (d, 1H, J = 16 Hz); 7.32-7.35 (m, 1H); 7.36-7.43 (m, 3H); 7.55-7.59 (m, 2H); 8.34 (d, 1H, J = 8.9 Hz).

Example 11. 1-[3-methyl-7-(allyloxy)flavon-8-yl]-3-(3,4,5-trimethoxy-phenyl)propen-1-one (see accompanying formula drawing VIB 171).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 7-allyloxy-8-acetyl-3-methylflavone (2.5 g, 0.0075 mol) and 3,4,5-trimethoxy-benzaldehyde

(1.47 g, 0.0075 mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified; the precipitate is separated by filtration and dried under vacuum. The compound is crystallized by methanol to give 2.4 g of product m.p.121-23°C, ^{1}H-NMR ($CDCl_3$) δ: 2.20 (s, 3H); 3.87 (m, 9H); 4.73 (d, 2H, J = 5,1 Hz; 5.25-5.45 (m, 2H); 5.91-6.02 (m, 1H); 6.75 (s, 2H); 6.96 (d,1H, J = 16 Hz); 7.10 (d, 1H, J = 8.9 Hz); 7.30 (d, 1H, J = 16 Hz); 7.42-7.46 (m, 3H); 7.55-7.59 (m, 2H); 8.34 (d, 1H, J = 8.9 Hz).

Example 12. 1-[3-methyl-7-(2-methylallyloxy)flavon-8-yl]-3-phenylpropen-1-one (see accompanying formula drawing VIB 165).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 7-(2-methylallyloxy)-8-acetyl-3-methylflavone (2.61 g, 0.0075 mol) and benzaldehyde (0.8 g, 0.0075 mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified; the precipitate is separated by filtration and dried under vacuum. The compound is crystallized by methanol to give 2.8 g of product m.p.145-47°C, ^{1}H-NMR ($CDCl_3$) δ:1.78 (s, 3H); 2.20 (s, 3H); 4.62 (s, 2H); 4.98 (d, 2H, J = 18 Hz); 7.06 (d,1H, J = 16 Hz); 7.09 (d, 1H, J = 8.9 Hz); 7.35-7.45 (m,7H); 7.50-7.55(m, 4H); 8.32 (d, 1H, J = 8.9 Hz).

Example 13. 1-[3-methyl-7-(2-methylallyloxy)flavon-8-yl]-3-(3-methoxy-phenyl)-propen-1-one (see accompanying formula drawing VIB 169).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 7-(2-methylallyloxy)-8-acetyl-3-methylflavone (2.61 g, 0.0075 mol) and 3-methoxy-benzaldehyde (1.01 g, 0.0075 mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified; the precipitate is separated by filtration and dried under vacuum. The compound is crystallized

by methanol to give 2.4 g of product m.p. 131-34°C, ^{1}H-NMR ($CDCl_3$) δ: 1.76 (s, 3H); 2.20 (s, 3H); 3.82 (s, 3H) 4.62 (s, 2H); 5.05 (d, 2H, J = 18 Hz); 6.95-7.10 (m, 3H); 7.09 (d, 1H, J = 9 Hz); 7.10 (d, 1H, J = 9 Hz); 7.31 (d, 1H, J = 16 Hz); 7.40-7.45 (m,3H); 7.55-7.58 (m, 2H); 7.31 (s, 2H); 8.32 (d, 1H, J = 8.9 Hz).

Example 14. 1-[3-methyl-7-(2-methylallyloxy)flavon-8-yl]-3-(3,4,5-trimethoxyphenyl)-propen-1-one (see accompanying formula drawing VIB 172).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 7-(2-methylallyloxy)-8-acetyl-3-methylflavone (2.61 g, 0.0075 mol) and 3,4,5-trimethoxy-benzaldehyde (1.47 g, 0.0075 mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified; the precipitate is separated by filtration and dried under vacuum. The compound is crystallized by methanol to give 2.4 g of product m.p. 82-84°C, ^{1}H-NMR ($CDCl_3$) δ:1.76 (s, 3H); 2.20 (s, 3H); 3.82 (s, 3H); 4.62 (s, 2H); 5.05 (d, 2H, J = 18 Hz) ; 6.95-7.10 (m,3H); 7.09 (d,1H); 7.10 (d,1H, J = 9 Hz); 7.31 (d, 1H, J = 16 Hz); 7.40-7.45 (m,3H); 7.55-7.58 (m, 2H); 7.31 (s, 2H); 8.32 (d, 1H, J = 8.9 Hz).

Example 15. 1-[3-methyl-7-(prop-2-ynyloxy)flavon-8-yl]-3-phenyl-propen-1-one (see accompanying formula drawing VIB 167).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 7-(prop-2-ynyloxy)-8-acetyl-3-methylflavone (2.49 g, 0.0075 mol) and benzaldehyde (0.8 g, 0.0075 mol) in ethanol 95%. The addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified; the precipitate is separated by filtration and dried under vacuum. The compound is crystallized by methanol to give 2.8 g of product m.p.157-59°C, ^{1}H-NMR ($CDCl_3$), δ: 2.20 (s, 3H); 2.56 (s, 1H); 4.86 (d, 2H, J = 2.2 Hz); 7.05 (d, **1H, J = 16 Hz);** 7.23 (d, **1H, J = 8.9 Hz); 7.31-7.50 (m, 7H);** *7.50-7.57* (m, H); 8,34 (d, 1H, J = 8.9 Hz).

Example 16. 1-[3-methyl-7-(prop-2-yny1oxy)flavon-8-yl]-3-(3,4,5~trimethoxy-phenyl)propen-1-one (see accompanying formula drawing VIB 174).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 7-(prop-2-ynyloxy)-8-acetyl-3-methylflavone (2.49 g, 0.0075 mol) and 3,4,5-trimethoxy-benzaldehyde (1.47 g, 0.0075 mol) in ethanol 95%. The addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified; the precipitate is separated by filtration and dried under vacuum. The compound is crystallized by methanol to give 2.8 g of product m.p.152-54°C, ^{1}H-NMR ($CDCl_3$) δ: 2.02 (s, 3H), 2.56 (m, 1H); 3.86 (m, 9H); 4.86 (d, 2H, J = 2.2 Hz); 6.75 (s, 2H); 6.98 (d, 1H, J = 16 Hz); 7.24-7.43 (m, 4H); 7.53-7.56 (m, 3H); 8.36 (d, 1H, J = 8.9 Hz).

Example 17. 1-[3-methyl-7-(3-methylbut-2-enyloxy)flavon-8-yl]-3-(2-thienyl)-propen-1-one (see accompanying formula drawing VIB 238).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 7-(3-methylbut-2-enyloxy)-8-acetyl-3-methylflavone (2.71g, 0.0075 mol) and 2-thiophene-carboxyaldehyde (0.84 g, 0.0075 mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified; the precipitate is separated by filtration and dried under vacuum. The compound is crystallized by methanol to give 2.5 g of product m.p. 158-160°C, ^{1}H-NMR ($CDCl_3$) δ: 1.58 (s, 3H), 2.07 (s, 3H), 4.6 (d, J=6.6 Hz, 2H), 5.3 (m, 1H), 6.65-818 (m, 12H).

Example 18. 1-[3-methyl-7-methoxyflavon-8-yl]-3-(4-cyanophenyl)-propen-1-one (see accompanying formula drawing VIB 247).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 7-methoxy-8-acetyl-3-methylflavone (2.31 g, 0.0075 mol) and 4-cyanobenzaldehyde (0.98 g, 0.0075 mol) in ethanol 95%; the addition is performed under energetic

stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified; the precipitate is separated by filtration and dried under vacuum. The compound is crystallized by ethanol to give 2.1 g of product m.p. 223-224°C, ^{1}H-NMR ($CDCl_3$) δ: 2.18 (s, 3H), 3.96 (s, 3H), 7.04-8.36 (m, 13H).

Example 19. 1-(2-Methylallyloxy-xanthen-9-one-4-yl)-3-(4-fluorophenyl)-propen-1-one (see accompanying formula drawing VIB 245).

A solution of KOH 50% (3ml) is added to an equimolar solution of 3-(2-methylallyloxy)-4-acetyl-xanthen-9-one (2.31 g, 0.0075 mol) and 4-fluoro-benzaldehyde (0.93 g, 0.0075 mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified; the precipitate is separated by filtration and dried under vacuum. The compound is crystallized by methanol to give 2.2 g of product m.p. 135-137°C, ^{1}H-NMR ($CDCl_3$) δ: 1.7 (m, 3H), 4.5 (m, 2H), 4.98 (m, 2H), 7.0-8.45 (m, 12H).

Example 20. 1-(2-Allyloxy-xanthen-9-one-4-yl)-3-(4-methylthiophenyl)propen-1-one (see accompanying formula drawing VIB 244).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 3-(allyloxy)-4-acetylxanthen-9-one (2.21 g, 0.0075 mol) and 4-methylthio-benzaldehyde (1.13 g, 0.0075 mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left stirring for one night and then diluted with water and acidified; the precipitate is separated by filtration and dried under vacuum. The compound is crystallized by methanol to give 2.1 g of product m.p. 142-144°C, ^{1}H-NMR ($CDCl_3$) δ: 2.49 (s, 3H), 4.7 (d, 2H), 5.3 (m, 2H), 5.9 (m, 1H), 7.03-8.41 (m, 12H).

Example 21. 1-[3-methyl-7-(3-methylbut-2-enyloxy)flavon-8-yl]-3-(4-chloro-phenyl)-propen-1-one (see accompanying formula drawing VIB 239).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 7-(3-methylbut-2-enyloxy)-8-acetyl-3-methylflavone (2.71 g, 0.0075 mol) and 4-chloro-benzaldehyde (1.05 g, 0.0075 mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified; the precipitate is separated by filtration and dried under vacuum. The compound is crystallized by methanol to give 1.9 g of product m.p. °C, ^{1}H-NMR ($CDCl_3$) δ: 1.69 (s, 3H), 1.72 (s, 3H), 2.19 (s, 3H), 4.65 (d, 2H), 5.31 (m, 1H), 6.97-8.42 (m, 13H).

Example 22. 1-(2-Methylallyloxy-xanthen-9-one-4-yl)-3-(2,6-dichloro-phenyl)-propen-1-one (see accompanying formula drawing VIB 246).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 3-(2-methylallyloxy)-4-acetyl-xanthen-9-one (2.31 g, 0.0075 mol) and 2,6-dichloro-benzaldehyde (1.31 g, 0.0075 mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified; the precipitate is separated by filtration and dried under vacuum. The compound is crystallized by methanol to give 2.1 g of product m.p. 135-137°C, ^{1}H-NMR ($CDCl_3$) δ: 4.74 (m, 2H), 5.4 (m, 2H), 5.95 (m, 1H), 7.06-8.5 (m, 11H).

BIOLOGICAL EVALUATION

Compounds VIB 167, VIB 178 and VIB 173 were tested for their cytotoxicity against drug-resistant cancer cells, both alone, and in combination with paclitaxel. The results of these studies are shown below.

When tested alone, compounds VIB 167, VIB 178 and VIB 173 were found to possess relatively low cytotoxicity (IC_{50} > 1 μM) against drug-resistant cancer cells.

The compounds were then evaluated in combination with paclitaxel for their cytostatic activity against the drug-resistant breast cancer cells MDA-435/LCC6-MDR.

In the experiments, the compounds were used in combination with paclitaxel, the paclitaxel being at a concentration of 0.3 μM. Paclitaxel used alone possesses an IC_{50} of 426 nM. However, as the results in Table 1 indicate, the IC_{50} of paclitaxel decreases by 5-20 fold when used in combination with each of VIB 167, VIB 178 and VIB 173., i.e. from 426 nM to 82-21 nM, compared with paclitaxel alone. Consequently, in the presence of these compounds, paclitaxel can recover its excellent inhibitory activity against the drug-resistant cancer cells.

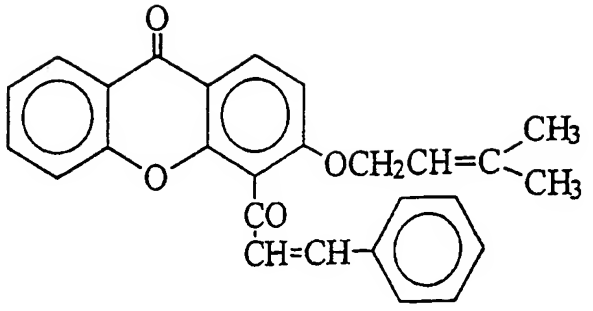
Compound	IC_{50}/nM	% Reduction in IC_{50} of paclitaxel
Paclitaxel	426	-
VIB 167 + Paclitaxel	82	80
VIB 178 + Paclitaxel	50	88
VIB 173 + Paclitaxel	21	95

Table 1

Experimental

The treatment consisted of concurrent exposure of MDA-435/LCC-MDR cells to paclitaxel in the presence or absence of the compounds reversing agent (1 μM) for 72 h *in vitro*. Assessment of cytotoxicity, i.e. cell growth inhibition, was determined according to the methods of Skehan, et al. as discussed in J. Nat. Cancer Inst., 82, 1107, 1990.

Briefly, cells were plated between 400 and 1200 cells/well in 96 well plates and incubated at 37°C for 15-18 h prior to drug addiction to allow attachment of cells. Compounds were solubilized in 100% DMSO and further diluted in RPMI-1640 containing 10 mM HEPES. After a 72 h incubation, 100 ml of ice-cold 50% TCA was added to each well and incubated for 1 h at 4°C. Plates were then washed 5 times with tap water to remove TCA, low-molecular weight metabolites and serum proteins. Sulforhodamine B (SRB) (0.4%, 50 ml) was added to each well. Following a five minute incubation at room temperature, plates were rinsed 5 times with 0.1% acetic acid and air dried. Bound dye was solubilized with 10 mM Tris Base (pH 10.5) for 5 min on a gyratory shaker. Optical density was measured at 570 nm.



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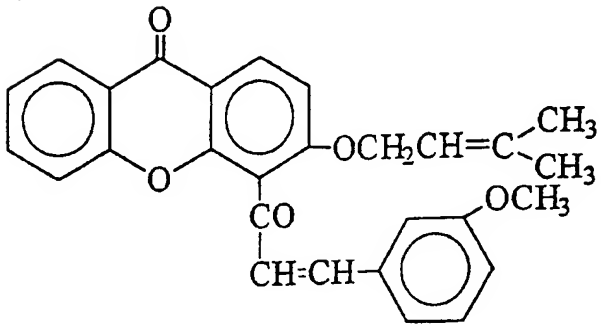

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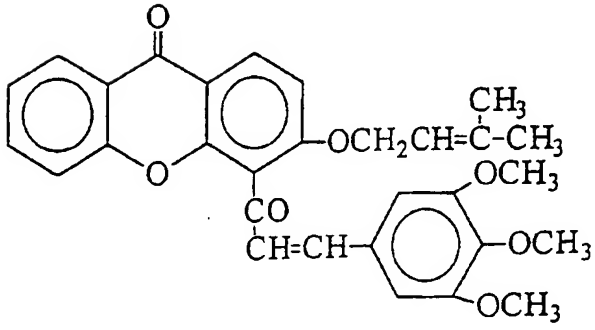

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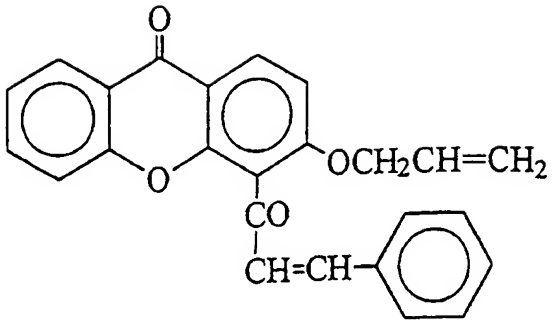

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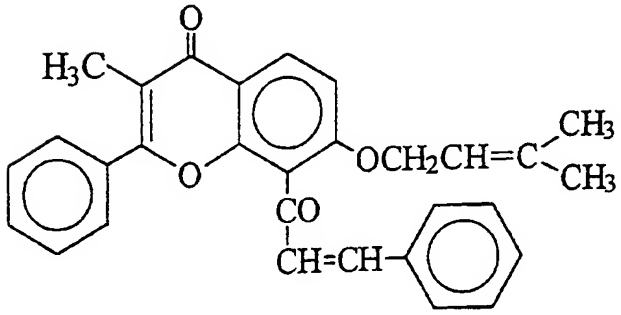

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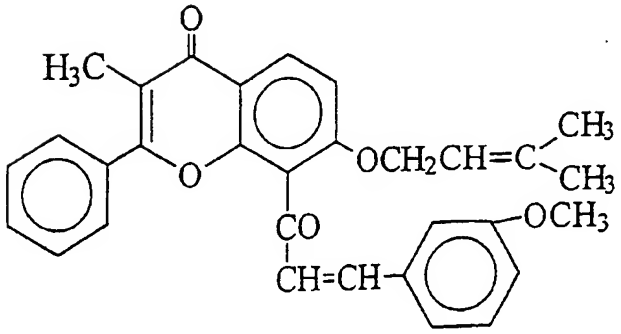

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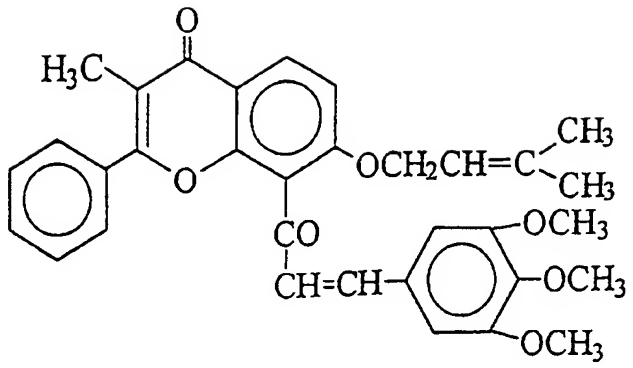

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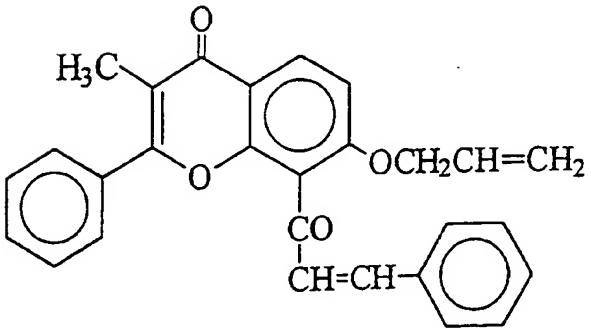

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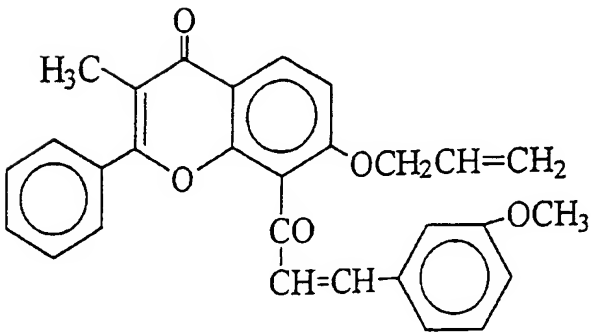

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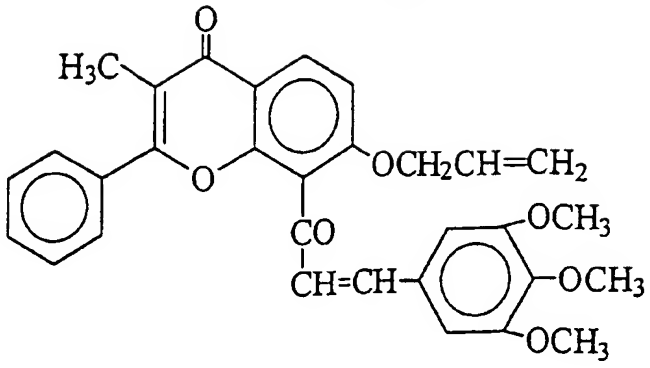

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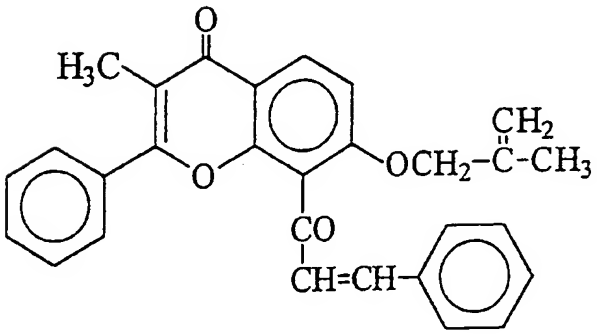

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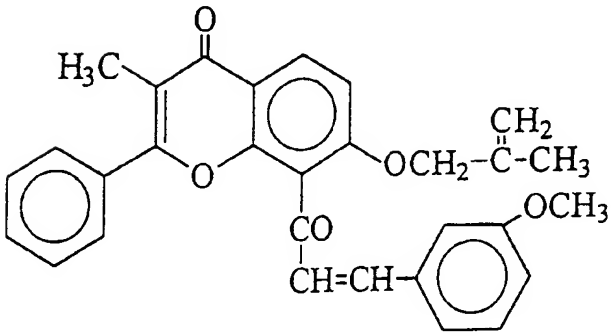

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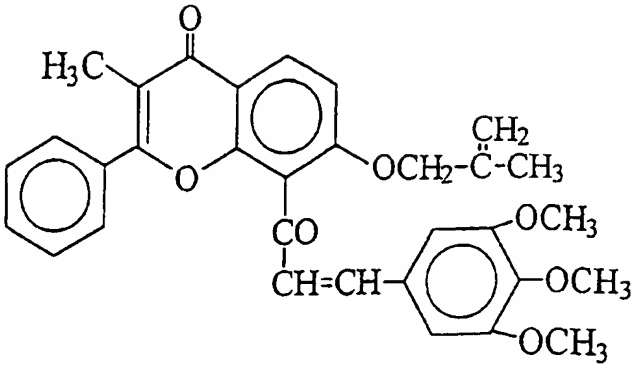

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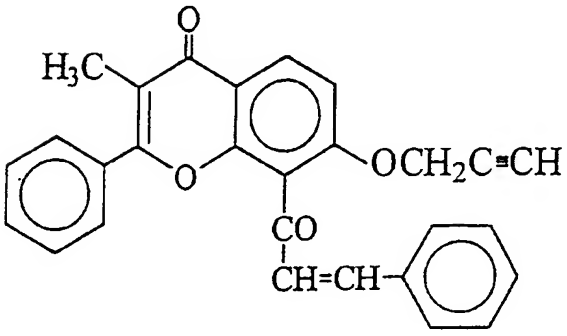

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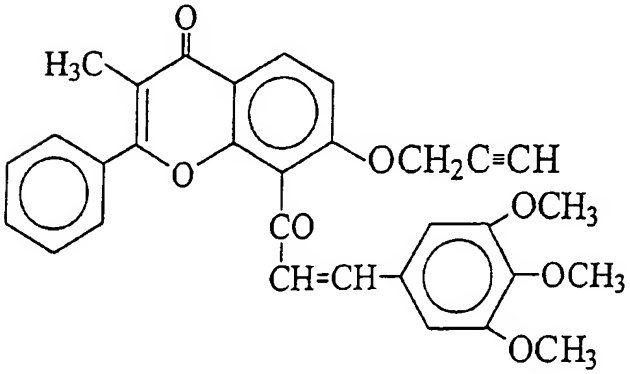

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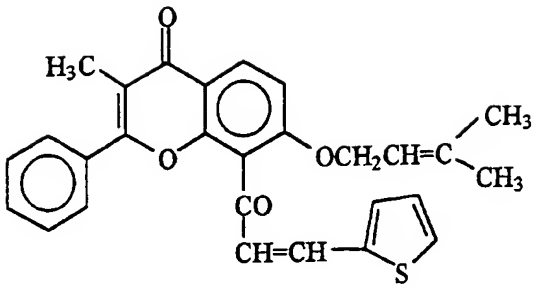

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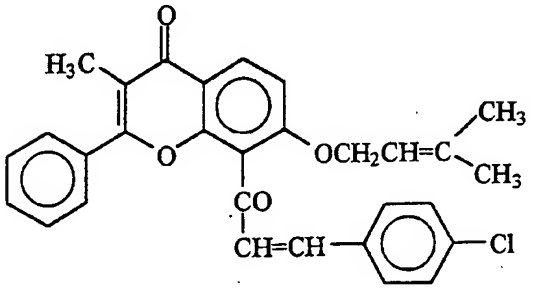

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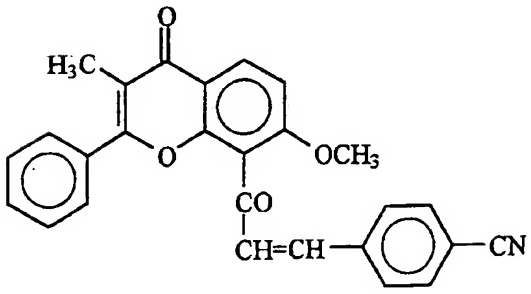
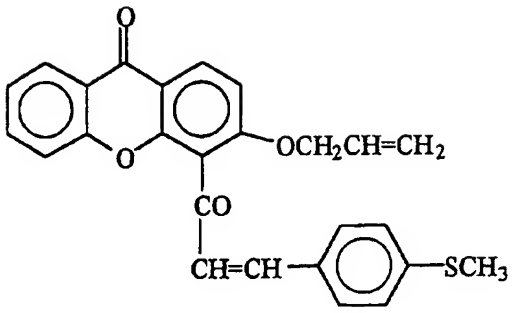


VIB 247



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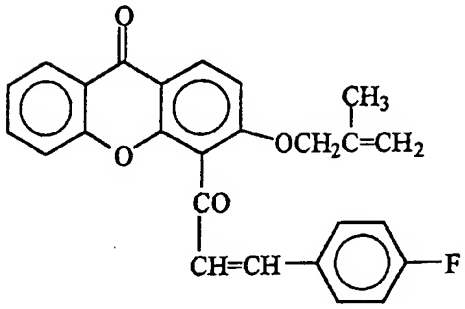

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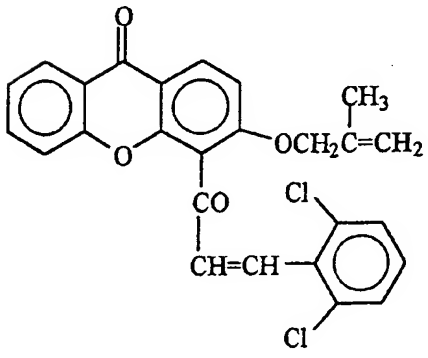

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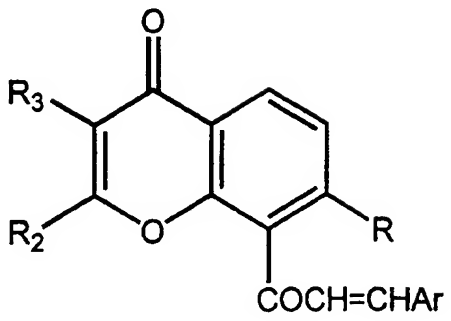
CLAIMS

1. A compound of Formula (I):



(I)

or a pharmaceutically acceptable salt or solvate thereof wherein:

Ar represents

a substituted or unsubstituted, (preferably aromatic), carbocyclic or heterocyclic group, said carbocyclic or heterocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings, wherein the or each ring contains 5 or 6 ring atoms, any heteroatoms being selected from N, O and S, any substituents on the Ar group being independently selected from the group consisting of:

(a) Cl, (b) Br, (c) F, (d) OH, (e) NO_2, (f) CF_3, (g) C_{1-4} lower alkyl (in particular CH_3), (h) SCH_3, (i) $NHCOCH_3$, (j) $N(R^6)(R^8)$ wherein R^6 and R^8 are the same or different and each represents H or lower C_{1-4} alkyl, (k) OR^{10} wherein R^{10} represents a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from:

Cl, Br, F, OMe, NO_2 and CF_3,

and (l) $-OCOR^{11}$, wherein R^{11} represents a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group or a phenyl group;

R represents

OH, OR^{10} or $OCOR^{11}$, wherein R^{10} and R^{11} are as defined above; and

(A) R^2 and R^3 are each independently selected from:

(i) a substituted or unsubstituted, preferably aromatic, carbocyclic or heterocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings, wherein the or each ring contains 5 or 6 ring atoms, any heteroatoms being selected from N, O and S, any substituents being independently selected from the group consisting of:

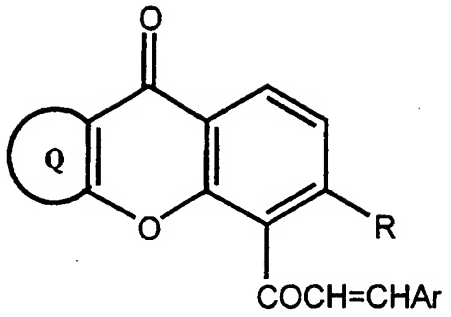
Cl, Br, F, OH, NO_2, CF_3, C_{1-4} lower alkyl (in particular CH_3), SCH_3, $NHCOCH_3$, $N(R^5)(R^8)$, OR^{10} and $OCOR^{11}$, wherein R^6, R^8, R^{10} and R^{11} are as defined above,

(ii) Cl, (iii) Br, (iv) F, (v) OH, (vi) NO_2, (vii) a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3, (viii) $NHCOCH_3$, (ix) $N(R^6)(R^8)$, (x) SR^{10}, (xi) OR^{10}, and (xii) $OCOR^{11}$ wherein R^6, R^8, R^{10} and R^{11} are as defined above;

or

(B) R_2 and R_3 taken together with the carbon atoms to which they are attached form a carbocyclic or heterocyclic ring having 5 or 6 ring atoms, any heteroatom being selected from N, O or S, said carbocyclic or heterocyclic ring being saturated or unsaturated, and being unsubstituted or substituted with one or more substituents selected from Cl, Br, F, OH, NO_2, CF_3, C_{1-4} lower alkyl, SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $OCOR^{11}$, wherein R^6, R^8, R^{10} and R^{11} are as defined above.

2. A compound of Formula (I) according to Claim 1 having the structure (IA):



(IA)

wherein the substituents R and Ar are as defined for Claim 1, and R^2 and R^3 taken together represent Ring Q, said Ring Q being a carbocyclic or heterocyclic ring having 5 or 6 ring atoms, any heteroatom being selected from N, O or S, said carbocyclic or heterocyclic ring being saturated or unsaturated and being unsubstituted or substituted with one or more substituents selected from: Cl, Br, F, OH, NO_2, CF_3, C_{1-4} lower alkyl, SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $OCOR^{11}$, wherein R^6, R^8, R^{10} and R^{11} are as defined as for Claim 1.

3. A compound of Formula (I) according to Claim 1, wherein R and Ar are as defined for Claim 1; and

R^2 and R^3 are each independently selected from:

(i) a substituted or unsubstituted, preferably aromatic, carbocyclic or heterocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings, wherein the or each ring contains 5 or 6 ring atoms, any heteroatoms being selected from N, O and S, any substituents being independently selected from the group consisting of:

Cl, Br, F, OH, NO_2, CF_3, C_{1-4} lower alkyl (in particular CH_3), SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $OCOR^{11}$, wherein R^6, R^8, R^{10} and R^{11} are as defined above,

(ii) Cl, (iii) Br, (iv) F, (v) OH, (vi) NO_2, (vii) a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3, (viii) $NHCOCH_3$, (ix) $N(R^6)(R^8)$, (x) SR^{10}, (xi) OR^{10}, and (xii) $OCOR^{11}$ wherein R^6, R^8, R^{10} and R^{11} are as defined in Claim 1.

4. A compound according to Claim 3 wherein R^2 represents a substituted or unsubstituted, preferably aromatic, carbocyclic or heterocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings, wherein the or each ring contains 5 or 6 ring atoms, any heteroatoms being selected from N, O and S, any substituents being independently selected from the group consisting of:

Cl, Br, F, OH, NO_2, CF_3, C_{1-4} lower alkyl (in particular CH_3), SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $OCOR^{11}$, wherein R^6, R^8, R^{10} and R^{11} are as defined in Claim 1.

5. A compound according to Claim 3 wherein R^3 is selected from the group consisting of:

Cl, Br, F, OH, NO_2, a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from:

Cl, Br, F, OMe, NO_2 and CF_3;

$NHCOCH_3$, $N(R^6)(R^8)$, SR^{10}, OR^{10} and $OCOR^{11}$, wherein R^6, R^8, R^{10} and R^{11} are as defined in Claim 1.

6. A compound according to Claim 3 wherein

R^2 represents

a substituted or unsubstituted, preferably aromatic, carbocyclic or heterocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings, wherein the or each ring contains 5 or 6 ring

atoms, any heteroatoms being selected from N, O and S, any substituents being independently selected from the group consisting of:

Cl, Br, F, OH, NO_2, CF_3, C_{1-4} lower alkyl (in particular CH_3), SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $OCOR^{11}$, wherein R^6, R^8, R^{10} and R^{11} are as defined in Claim 1; and

R^3 is selected from the group consisting of:

Cl, Br, F, OH, NO_2, a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from:

Cl, Br, F, OMe, NO_2 and CF_3,

$NHCOCH_3$, $N(R^6)(R^8)$, SR^{10}, OR^{10} and $OCOR^{11}$, wherein R^6, R^8, R^{10} and R^{11} are as defined in Claim 1.

7. A compound according to any preceding claim wherein R^3 is selected from: Cl, Br, F, OH, NO_2, CF_3, C_{1-4} lower alkyl, SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10}, and $OCOR^{11}$ wherein R^6, R^8, R^{10} and R^{11} are as defined in Claim 1.

8. A compound according to Claim 7 wherein R^3 is a C_{1-4} lower alkyl group.

9. A compound according to Claim 8 wherein R^3 is methyl.

10. A compound according to any preceding claim wherein R^2 is a substituted or unsubstituted, preferably aromatic, carbocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings, wherein the or each ring contains 5 or 6 ring atoms, and any substituents are independently selected from the group consisting of:

Cl, Br, F, OH, NO_2, CF_3, C_{1-4} lower alkyl (in particular CH_3), SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $OCOR^{11}$, wherein R^6, R^8, R^{10} and R^{11} are as defined in Claim 1.

11. A compound according to Claim 10 wherein R^2 is an unsubstituted, preferably aromatic, carbocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings, wherein the or each ring contains 5 or 6 ring atoms.

12. A compound according to Claim 11 wherein R^2 is phenyl.

13. A compound according to any preceding claim wherein R^{10} and R^{11} represents a saturated or unsaturated C_{1-6} straight chain or branched hydrocarbyl group.

14. A compound according to Claim 13 wherein R^{10} and R^{11} are selected from methyl, ethyl, n-propyl and iso-propyl.

15. A compound according to any preceding claim wherein R represents $-OCH_2CH=CMe_2$, $-OCH_2CMe=CH_2$, $-OCH_2CH=CH_2$ or $-OCH_2C{\equiv}CH$.

16. A compound according to any preceding claim wherein the group Ar represents phenyl which may be unsubstituted or substituted with one or more substituents selected from the group consisting of Cl, Br, F, OH, NO_2, CF_3, C_{1-4} lower alkyl (in particular CH_3), SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $OCOR^{11}$ wherein R^6, R^8, R^{10} and R^{11} are as defined as for Claim 1.

17. A compound according to any preceding claim wherein Ar represents phenyl or phenyl substituted with 1, 2 or 3 methoxy groups.

18. A compound according to any preceding claim wherein Ar is selected from trimethoxyphenyl, 3-pyridyl, 4-pyridyl and 3-indolyl; and R is selected from $OCH_2CH=CMe_2$, $OCH_2CMe=CH_2$, $OCH_2CH=CH_2$ and $OCH_2C{\equiv}CH$.

19. A compound according to any preceding claim wherein

Ar represents

phenyl, which may be unsubstituted or substituted by one, two or three substituents independently selected from

Cl, Br, F, OMe, NO_2, CF_3, C_{1-4} lower alkyl (in particular CH_3), NMe_2, NEt_2, SCH_3 and $NHCOCH_3$;

thienyl, 2-furyl, 3-pyridyl, 4-pyridyl or indolyl.

R represents

OH or OCH_2R^1, wherein R^1 is selected from $-CH=CMe_2$, $-CMe=CH_2$, $-CH=CH_2$ and $-C\equiv CH$.

20. A compound according to any of Claims 1 to 15 wherein the group Ar is a substituted or unsubstituted, preferably aromatic, heterocyclic group, said heterocyclic group containing from 5 to 10 ring atoms, at least one of which is a nitrogen atom, said ring atoms forming one or two rings, with the or each ring containing 5 or 6 ring atoms, wherein any substituent on the ring is as defined as for Claim 1.

21. A compound according to any of Claims 1 to 15 wherein the group Ar is substituted with at least one substituent selected from $NHCOCH_3$ or $N(R^6)(R^8)$, wherein R^6 and R^8 are the same or different and each represents H or lower C_{1-4} alkyl.

22. A compound according to any of Claims 1-15 wherein Ar is selected from the group consisting of 3-pyridyl, 4-pyridyl, 3-indolyl, 4-dimethyl-aminophenyl and 4-acetamidophenyl.

23. A compound of Formula (I) selected from the following:

1-[3-(3-methylbut-2-enyloxy)xanthen-9-one-4-yl]-3-phenyl-propen-1-one (VIB 176),

1-[3-(3-methylbut-2-enyloxy)xanthen-9-one-4-yl]-3-(3-methoxy-phenyl)-propen-1-one (VIB 177),

1-[3-(3-methylbut-2-enyloxy)xanthen-9-one-4-yl]-3-(3,4,5-tri-methoxyphenyl)-propen-1-one (VIB 178),

1-[3-(allyloxy)xanthen-9-one-4-yl] -3-phenyl-propen-1-one (VIB 175),

1-[3-methyl-7-(3-methylbut-2-enyloxy)flavon-8-yl]-3-phenyl-propen-1-one (VIB 166),

1-[3-methyl-7-(3-methylbut-2-enyloxy)flavon-8-yl]-3-(3-methoxy)phenyl-propen-1-one (VIB 170),

1-[3-methyl-7-(3-methylbut-2-enyloxy)flavon-8-yl]-3-(3,4,5-tri-methoxy)phenyl-propen-1-one (VIB 173),

1-[3-methyl-7-(allyloxy)flavon-8-yl]-3-phenyl-propen-1-one (VIB 164),

1-[3-methyl-7-(allyloxy)flavon-8-yl)-3-(3-methoxyphenyl)-propen-1-one (VIB 168),

1-[3-methyl-7-(allyloxy)flavon-8-yl]-3-(3,4,5-trimethoxy-phenyl)propen-1-one (VIB 171),

1-[3-methyl-7-(2-methylallyloxy)flavon-8-yl]-3-phenylpropen-1-one (VIB 165),

1-[3-methyl-7-(2-methylallyloxy)flavon-8-yl]-3-(3-methoxy-phenyl)-propen-1-one (VIB 169),

1-[3-methyl-7-(2-methylallyloxy)flavon-8-yl]-3-(3,4,5-tri-methoxyphenyl)-propen-1-one (VIB 172),

1-[3-methyl-7-(pro-2-ynyloxy)flavon-8-yl]-3-phenyl-propen-1-one (VIB 167) and

1-[3-methyl-7-(pro-2-yny1oxy)flavon-8-yl]-3-(3,4,5~trimethoxy-phenyl-propen-1-one (VIB 174).

24. A compound of Formula (I) as defined in any preceding claim for use as an antiproliferative medicament.

25. Use of a compound of Formula (I) as defined in any preceding claim for the manufacture of a medicament for the treatment or prevention of neoplasms.

26. Use according to Claim 25 wherein the neoplasms are located in the uterus, ovary or breast.

27. Use according to Claim 25 or 26 of a compound of Formula (I) for the manufacture of a medicament for the treatment of paclitaxel- and docetaxel-resistant cancer cells.

28. Use according to any of Claims 25 to 27 of a compound of Formula (I) in the manufacture of an antiproliferative medicament for combination therapy.

29. Use according to any of Claims 25 to 28 of a compound of Formula (I) in the manufacture of an antiproliferative medicament in combination with one or more antineoplastic agents.

30. The use according to Claim 29 wherein the antineoplastic agent comprises paclitaxel or docetaxel.

31. The use according to Claim 25 in the manufacture of a medicament for the treatment or prevention of menopausal disorders and osteoporosis.

32. A pharmaceutical composition comprising one of more of the compounds of Formula (I) as defined in any preceding claim, in combination with one or more pharmaceutically acceptable excipients.

33. A pharmaceutical composition according to Claim 32 further comprising one or more antineoplastic agents.

34. A pharmaceutical composition according to Claim 32 wherein the antineoplastic agent is selected from paclitaxel or docetaxel.

INTERNATIONAL SEARCH REPORT

Inte .donal Application No
PCT/EP 00/08366

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D311/86 C07D311/30 C07D409/06 A61K31/37 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 116, no. 12, 30 March 1992 (1992-03-30) Columbus, Ohio, US; abstract no. 128767, SHANKER, M. S. S. ET AL: "A novel synthesis of pyrazolylchromone derivatives" XP002159498 abstract & ASIAN J. CHEM. (1992), 4(1), 166-70 , --- -/--	1-22

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 February 2001	19/02/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Beslier, L

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INTERNATIONAL SEARCH REPORT

Intl. Jonal Application No
PCT/EP 00/08366

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 112, no. 19, 7 May 1990 (1990-05-07) Columbus, Ohio, US; abstract no. 178917, SHANKER, M. S. S. ET AL: "Synthesis and cleavage reactions of benzothiazepinylchromone derivatives" XP002159499 abstract & PHOSPHORUS, SULFUR SILICON RELAT. ELEM. (1989), 44(1-2), 143-7 , ---	1-22
X	CHEMICAL ABSTRACTS, vol. 112, no. 5, 29 January 1990 (1990-01-29) Columbus, Ohio, US; abstract no. 35634, SHANKAR, M. S. S. ET AL: "Synthesis of a new series of chromonyl chalcones" XP002159500 abstract & J. INDIAN CHEM. SOC. (1989), 66(1), 30-1 , ---	1-22
A	WO 96 19209 A (INDENA S.P.A.) 27 June 1996 (1996-06-27) cited in the application the whole document ---	1,24-34
A	WO 91 17749 A (BAYLOR COLLEGE OF MEDICINE) 28 November 1991 (1991-11-28) cited in the application the whole document ---	1,24-34
A	WO 96 22985 A (WARNER-LAMBERT CO.) 1 August 1996 (1996-08-01) the whole document -----	1,24-34

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ..tional Application No
PCT/EP 00/08366

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9619209 A	27-06-1996	IT MI942568 A	20-06-1996
		AU 689357 B	26-03-1998
		AU 4301996 A	10-07-1996
		CA 2208351 A	27-06-1996
		CN 1170362 A	14-01-1998
		CZ 9701869 A	12-11-1997
		EP 0800387 A	15-10-1997
		FI 972641 A	14-08-1997
		HU 77438 A	28-04-1998
		JP 10511346 T	04-11-1998
		NO 972842 A	19-06-1997
		PL 320787 A	27-10-1997
		SI 9520139 A,B	31-10-1997
		SK 78197 A	10-12-1997
		US 5808137 A	15-09-1998
WO 9117749 A	28-11-1991	AU 7963691 A	10-12-1991
		CA 2084208 A	18-11-1991
		EP 0528975 A	03-03-1993
		JP 5509078 T	16-12-1993
WO 9622985 A	01-08-1996	US 5525625 A	11-06-1996
		AT 181913 T	15-07-1999
		AU 690400 B	23-04-1998
		AU 4245696 A	14-08-1996
		CA 2208075 A	01-08-1996
		DE 69510696 D	12-08-1999
		DE 69510696 T	23-12-1999
		DK 805807 T	17-01-2000
		EP 0805807 A	12-11-1997
		ES 2137554 T	16-12-1999
		GR 3031295 T	31-12-1999
		JP 10512878 T	08-12-1998
		NZ 297320 A	28-05-1999
		ZA 9600528 A	15-08-1996